REMARKS

Claims 1 and 8-22 are currently pending. The amendments of the claims are provided to assist the examiner in better understanding the invention. The claim amendments do not raise any issue of new matter. Newly added claims 14 and 20, reciting SEQ ID NO: 5, is supported throughout the specification, including at page 5, paragraph [0021]. Newly added claims 15, 16, 21, and 22, reciting SEQ ID NO: 4, is supported throughout the specification, including at page 5, paragraph [0021].

Applicants respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Rejection under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims and 8-13 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the present invention.

A. Claim 1

Claim 1 is rejected for allegedly failing to define the term "an enzyme" as recited in the claim. Applicants respectfully disagree because claim 1 clearly defines the claimed enzyme as an enzyme that cleaves a probe of SEQ ID NO: 3 when said probe is hybridized to HCV nucleic acids ("...an enzyme that cleaves said probe when said probe hybridizes to said HCV nucleic acids"). The language of claim 1 clearly describes the claimed enzyme's function, and would be readily understood by one of ordinary skill in the art. Thus, Applicants respectfully assert that the term "an enzyme" is properly defined in claim 1. Additionally, the instant specification provides a clear definition for the term "enzyme" used in claim 1. For example, on pages 7-8 in paragraph [0028], the specification provides a description of the claimed enzyme and an example of such an enzyme ("...a polymerase, such as rTth, having 5'-3' nuclease activity, ...cleaves the fluorogenic probe if it is bound specifically to the target nucleic acids..."). "If the claims when read in light of the specification reasonable apprise those skilled in the art of the scope of the invention, § 112 demands no more." *Miles Laboratories Inc. v. Shandon* 997 F.2d 870 (Fed. Cir. 1993).

The Examiner has suggested that Applicants claim a particular enzyme. However, Applicants respectfully draw the Examiner's attention to MPEP 2173.04, which states that the breadth of a claim is not to be equated with indefiniteness ("if the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph"). The recitation of claim 1 clearly describes the enzyme and its function and the specification provides additional supporting description. Thus, there is not need to limit the claim to a particular enzyme to meet the requirement of Section 112, second paragraph.

Because the recitation of claim 1 clearly describes the enzyme and its function and because the specification provides a description of the enzyme and an example of such an enzyme, claim 1 distinctly claims the subject matter of the invention. Therefore, Applicants respectfully assert that the rejection of claim 1 is inappropriate, and accordingly, Applicants request withdrawal of the rejection.

B. Claims 9, 10, 11, and 12

Claims 9, 10, 11, and 12 are rejected because the recited limitation of "step (a)" allegedly lacks antecedent basis. In light of the amendment to claims 9, 11, and 12 submitted herein, the rejection is rendered moot.

Applicants however, respectfully disagree with the basis for the rejection. First, Applicants note that the limitation of "step (a)" is not recited in claim 11. Thus, the rejection is improperly applied to claim 11. Furthermore, claim 10 depends on claim 9, and claim 9 and 12 depend on claim 8. However, claim 8 depends on claim 1. 37 C.F.R. § 1.75(c) states that "claims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim." Accordingly, the limitations of claim 1 including "step (a)" are incorporated into claims 8, 9, 10, and 12, thereby providing antecedent basis for the recited limitation of "step (a)," Therefore, Applicants respectfully assert that the rejection of claims 9, 10, 11, and 12 is inappropriate.

C. Claim 13

Claim 13 is rejected because the recited limitation of "lambda phage-HCV ribonucleic acid hybrids" allegedly lacks antecedent basis. Applicants respectfully point out that the rejection is without basis because claim 13 is dependent on claim 12, not claim 2. However, in light of the amendment to claim 13 submitted herein, the rejection is rendered moot.

II. Rejection under 35 U.S.C. § 103(a)

Claims 1 and 8-13 are rejected for allegedly being unpatentable over Kleiber et al. (J. Molecular Diagnosis, 2(3): 158-166, (2000)), Kawai et al. (J. Medical Virology, 58: 121-126, (1999)), Resnick et al. (USP 5,527,669), Michinori et al. (JP 103899), Sherer et al. (Nucleic Acids Research, 5: 3141-3156, (1978)), and Lee et al. (USP 6,316,610). Applicants respectfully assert that a *prima facie* case of obviousness has not been established because none of the above cited references, taken singly or in combination, teach or suggest all of the recited limitations of the presently claimed invention.

A. The Claimed Subject Matter

Claim 1 is directed to a method of detecting the presence of HCV nucleic acids in a test sample by (a) reverse transcribing and amplifying HCV in the test sample with a pair of primers corresponding to SEQ ID NOs: 1 and 2; (b) hybridizing the amplified HCV nucleic acid with a labeled probe having a nucleotide sequence consisting of SEQ ID NO: 3 in the presence of an enzyme that cleaves the labeled probe when it hybridizes to the amplified HCV nucleic acid; and (c) detecting the label.

Claim 18 is directed to a method for detecting the presence or amount of HCV nucleic acids in a test sample by (a) adding lambda phage-HCV nucleic acid hybrids to a test sample and reverse transcribing and amplifying HCV and in the test sample and lambda phage-HCV nucleic acid hybrids, both amplified with a pair of primers corresponding to SEQ ID NOs: 1 and 2; (b) hybridizing HCV amplicons with an oligonucleotide probe having a sequence consisting of SEQ ID NO:3 in the presence of an enzyme that cleaves said oligonucleotide probe when said probe hybridizes to said HCV nucleic acids, wherein said oligonucleotide probe is conjugated to a first detectable label that generates a detectable signal upon said cleavage; c) hybridizing lambda

phage-HCV hybrid amplicons to a control oligonucleotide probe has the sequence set forth in SEQ ID NO: 6 in the presence of an enzyme that cleaves said the control oligonucleotide probe when said control probe hybridizes to said lambda phage-HCV hybrid amplicons, wherein said control probe is conjugated to a second detectable signal that generates a detectable signal upon said cleavage; and d) separately detecting a signal from said first and second detectable labels, wherein said signal from said first detectable label indicates the presence or amount of HCV nucleic acids in said test sample.

B. The Cited References

Kleiber et al. teaches a reverse transcription-PCR assay for quantifying HCV RNA using the TaqMan principle. As admitted by the Patent Office, Kleiber et al. does not teach amplifying HCV with primers corresponding to SEQ ID NOs: 1 and 2 (see Official Action, page 5, item 12). Also admitted by the Patent Office, Kleiber et al. does not teach hybridization of the amplified HCV nucleic acid with a probe corresponding to SEQ ID NO: 3, let alone a probe of SEQ ID NO: 3 containing VIC or TAMRA. Furthermore, Kleiber et al. does not teach introducing lambda phage-HCV nucleic acids to a test sample, wherein the produced amplicons would hybridize to a control labeled probe corresponding to SEQ ID NO: 6. Instead, Kleiber et al. teaches adding an internal control probe that has primer regions that are identical to HCV (see Kleiber at page 159, paragraph 2).

Kawai et al. also teaches a reverse transcription-PCR assay for quantifying HCV RNA using the TaqMan principle. However, Kawai et al. does not teach amplifying HCV with primers corresponding to SEQ ID NOs: 1 and 2 (see Kawai at page 122, paragraph 4). In addition, Kawai et al. does not teach hybridization of the amplified HCV nucleic acid with a probe corresponding to SEQ ID NO: 3, let alone a probe of SEQ ID NO: 3 containing VIC or TAMRA. Furthermore, Kawai et al. does not teach introducing lambda phage nucleic acids to a test sample, wherein the produced amplicons would hybridize to a control labeled probe corresponding to SEQ ID NO:6.

Resnick et al. teaches PCR amplification of HCV nucleic in a test samples using primers corresponding to SEQ ID NOs: 1 and 2 of the instant specification (SEQ ID NOs: 1 and 2 of the

instant specification corresponds to SEQ ID NOs: 5 and 18, respectively of Resnick et al.). However, Resnick et al. does not teach hybridizing the amplified HCV nucleic acid with a labeled probe corresponding to SEQ ID NO: 3 in the presence of an enzyme that cleaves the labeled probe when it hybridizes to the amplified HCV nucleic acid, *e.g.* TaqMan RT-PCR. Furthermore, Resnick et al. does not teach introducing lambda phage-HCV nucleic acids to a test sample, wherein the produced amplicons would hybridize to a control labeled probe corresponding to SEQ ID NO:6.

Michinori et al. (11-103899) appears to be a publication from the Japanese Patent Office which is entirely in Japanese. Applicants disagree with the Examiner's assertion that Michinori et al. discloses a probe "used for detection of HCV RNA suitable for a fluorescence dye labeling." According to the Examiner, this information is found at line 7 on page 10 of the reference. However, the copy of JP 103899 provided by the Examiner ends at page 8. Reference to page and line numbers suggests that the Examiner is using a document other than the Japanese patent, which is laid out in columns. The Examiner has not provided an English translation of any portion of Michinori et al. so it is unclear how the Examiner has made the asserted determination. If the Examiner is referring to an English translation of Michinori et al. in the Office Action, Applicants request that such translation be provided to Applicants so that they have the opportunity to sufficiently evaluate and respond.

Michinori et al. does not disclose a labeled probe consisting of the sequence set forth in SEQ ID NO: 3, as is presently claimed. In addition, Michinori et al. teach hybridizing amplified HCV nucleic acid with a labeled probe corresponding to SEQ ID NO: 3 in the presence of an enzyme that cleaves the labeled probe when it hybridizes to the amplified HCV nucleic acid. Instead, Michinori et al. discloses a probe which *comprises* the nucleic acid sequence of SEQ ID NO: 3. However, as explicitly recited, step (b) of claim 1 is directed to "an oligonucleotide probe consisting of the sequence set forth in SEQ ID NO: 3" and not a probe comprising SEQ ID NO: 3. Furthermore, it does not appear that Michinori et al. teaches amplifying HCV with primers corresponding to SEQ ID NOs: 1 and 2 nor teaches introducing lambda phage nucleic acids to a test sample, wherein the produced amplicons would hybridize to a control labeled probe corresponding to SEQ ID NO:6.

Scherer et al. teaches the genomic structure and sequence of lambda phage. However, the Examiner has failed to particularly point out where Scherer teaches or suggests to use SEQ ID NO: 6 to generate a lambda phage-HCV hybrid. Also, Scherer et al. does not teach amplifying HCV with primers corresponding to SEQ ID NOs: 1 and 2. In addition, Scherer et al. does not teach hybridization of the amplified HCV nucleic acid with a probe corresponding to SEQ ID NO: 3, let alone a probe of SEQ ID NO: 3 containing VIC or TAMRA. Furthermore, Scherer et al. does not teach introducing lambda phage nucleic acids to a test sample, wherein the produced amplicons would hybridize to a control labeled probe corresponding to SEQ ID NO:6.

Lee et al. discloses a method of conjugating fluorescent and quencher dyes, such as VIC and FAM to oligonucleotides. Lee et al. does not teach amplifying HCV with primers corresponding to SEQ ID NOs: 1 and 2. In addition, Lee et al. does not teach hybridization of the amplified HCV nucleic acid with a probe corresponding to SEQ ID NO: 3. Furthermore, Lee et al. does not teach introducing lambda phage nucleic acids to a test sample, wherein the produced amplicons would hybridize to a control labeled probe corresponding to SEQ ID NO:6.

C. Applicants' response to the Examiner's allegations

The Examiner alleges that one of ordinary skill would have been motivated by the combined references of Kleiber et al., Kawai et al., Resnick et al., Michinori et al., Sherer et al., and Lee et al. to establish a method of detecting HCV RNA in a sample. Specifically, the Examiner alleges that it would have been obvious to (a) substitute the pair of probes disclosed in Resnick et al. with a pair of primers "more suitable for detecting broad strains of HCV"; (b) select a probe of SEQ ID NO: 1, as disclosed in Michinori et al.; and (c) select an internal control probe "specific to lambda phage T7 polymerase promoter region that is operably linked to the targeted HCV sequence disclosed by Sherer et al." Furthermore, the Examiner alleges that "Kleiber et al. teaches that the IC specific probe should be specific for the IC but not for the HCV" (see Official Action at page 6 in item 18). Moreover, the Examiner asserts that "any probe selected according to the disclosure of a full length lambda phage DNA sequence would be obvious for [a] person with ordinary skill" to use as an internal positive control (Office Action at page 5, item 16). Applicants respectfully disagree with all of the Examiner's allegations and address each of the Examiner's allegations in the discussion below.

In regards to the Examiner's allegation that it would have been obvious to substitute the pair of probes disclosed in Resnick et al. with a pair of primers "more suitable for detecting broad strains of HCV", Applicants respectfully disagree because this allegation is unsupported by any objective evidence and taken to its logical conclusion, the Examiner's position renders any of the many thousands of potential primer sequences that might be obtained from a large nucleic acid molecule automatically *prima facie* obvious, without any need to provide evidence that any particular sequence will function as a primer at all. Moreover, the Examiner's allegation is contrary to the understanding of those skilled in the art. Rather, the skilled artisan is well aware that each potential primer in a given nucleic acid sequence is not structurally or functionally equivalent.

To support Applicants rebuttal of the Examiner's unsupported premise that any pair of primers that can detect broad strains of HCV is an obvious substitution in an amplification process, Applicants submit Wang et al., *BioTechniques* 17: 82-87 (1994) which discusses the importance of particular primer pairs in the sensitivity of detecting target nucleic acids in PCR. The disclosure of Wang et al. notes that primers that differ even "slightly" in position can exhibit 100- to 1000-fold differences in amplification sensitivity (see abstract). Indeed, Wang et al. describes that "a dramatic improvement of the sensitivity was obtained by **new combinations of primers**..." (see p. 82, paragraph 2; emphasis added in bold). Furthermore, Wang et al. directly contradicts the Examiner's allegation that substitution of any primer pair is obvious to one of ordinary skill in the following statement:

> Our results suggest that primers are decisive for the sensitivity of PCR, and that there is **no reliable means to predict the sensitivity achieved by a given primer pair**. Some primer pairs, which have been designed taking into account the basic rules, **do not work** as efficiently as expected. **An extensive search** for optimal reaction protocol **may be unfruitful** with these primers. (p. 85, paragraph 5; emphasis added in bold)

Thus, the Examiner's notion that any primer pair can be substituted in an amplification of a target nucleic acid is incorrect and runs contrary to the understanding of an ordinary skilled artisan, as evidenced, for example, by the above citations from Wang et al.

In regards to the Examiner's allegation that it would have been obvious to "select a probe of SEQ ID NO: 1 as disclosed in Michinori et al. which is within the region amplified by the two primer" (Official Action, page 6, item 18), Applicants respectfully disagree because SEQ ID NO: 1 of Michinori et al. does not anticipate a probe consisting of SEQ ID NO: 3, as is presently claimed. Michinori et al. discloses a probe which *comprises* the nucleic acid sequence of SEQ ID NO: 3. However, as explicitly recited, step (b) of claim 1 is directed to "an oligonucleotide probe consisting of the sequence set forth in SEQ ID NO:3" and not a probe comprising SEQ ID NO: 3. "To establish *prima facie* obviousness of a claimed invention, **all** of the claim limitations must be taught or suggested by the prior art" (MPEP 2143.04, emphasis added in bold). Thus, SEQ ID NO: 1 of Michinori et al. does not render obvious the presently claimed method since Michinori et al. does not teach a probe consisting of SEQ ID NO: 3.

In regards to the Examiner's allegation that it would have been obvious to select an internal control probe "specific to lambda phage T7 polymerase promoter region that is operably linked to the targeted HCV sequence disclosed by Sherer et al." (Official Action, page 6, item 18). "The **teaching or suggestion to make the claimed combination** and the reasonable expectation of success **must both be found in the prior art, not in applicant's disclosure**" (MPEP 2143; emphasis added in bold). Contrary to the Examiner's assertion, neither Sherer et al. nor any reference cited by the Examiner teaches or suggests using an internal control probe that is specific to the lambda phage T7 polymerase promoter region. However, the instant specification teaches the advantages of introducing T7 promoter sequence into control amplicons as a convenient means of producing transcripts of the control amplicon nucleotides.

> By introducing T7 promoter sequences into the control amplicon and ultimately into the control RNA, the control can be introduced into test samples, reverse transcribed and amplified by the same primers used to reverse transcribe and amplify the target HCV sequences, providing a convenient positive control. (Specification, page 4, paragraph [0014]).

Indeed, the disclosure of Sherer et al. and any reference cited by the Examiner is silent to the advantages of introducing T7 promoter sequences into control lambda phage amplicons taught by Applicants' specification. Since the Examiner has evaluated the disclosure of Sherer et

al. using impermissible hindsight from Applicants' specification, Applicants respectfully submit that the Examiner's assertion is not only incorrect, but also inappropriate.

In regards to the Examiner's allegation that "Kleiber et al. teaches that the IC specific probe should be specific for the IC but not for the HCV" (see Official Action at page 6 in item 18), Applicants respectfully disagree because, contrary to the Examiner's allegation, there is no teaching that an internal control (IC) specific probe should be specific for the IC but not for the HCV in the disclosure of Kleiber et al. Instead, Kleiber et al. teaches that the "IC is an RNA transcript with primer regions identical to those of the HCV target and a unique probe region" (Kleiber et al, page 159, paragraph 1) but Kleiber et al. does not provide any teaching on the specificity of the IC probe.

In regards to the Examiner assertion that "any probe selected according to the disclosure of a full length lambda phage DNA sequence would be obvious for [a] person with ordinary skill" to use as an internal positive control (Office Action at page 5, item 16), Applicants respectfully disagree. First, the disclosure of Scherer et al. does not provide any teaching or suggestion to support the assertions that any lambda phage DNA sequence can be used as an internal positive control in the instantly claimed method or that every sequence in lambda phage DNA would work equally well as SEQ ID NO:6 in the instantly claimed method. Secondly, the Examiner has failed to provide any objective evidence. The Examiner's failure to provide this evidence fails to meet the burden of establishing a *prima facie* rejection.

D. Analysis of Non-Obviousness

"To establish a *prima facie case* of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations" (MPEP 2143). Applicants respectfully submit that none of these three criteria for the reasons described below and therefore, the Examiner has not met the burden of establishing a *prima facie case* of obviousness.

There is no suggestion or motivation to combine the teachings of the cited references. First, neither Kleiber et al. nor Kawai et al., both references which teach a reverse transcription-PCR assay for quantifying HCV RNA using the TaqMan principle, provide any suggestion or motivation to use the primer sequences taught in Resnick et al. In fact, Applicants have provided a reference by Wang et al. which **teaches away** from the notion that any primer pair can be substituted in a particular amplification process for detection of a target nucleic acid (see citation from Wang et al. discussed above). Secondly, neither Kleiber et al. nor Kawai et al. provide any suggestion or motivation to use an oligonucleotide probe consisting of SEQ ID NO: 3. Michinori et al. does not disclose an oligonucleotide probe consisting of SEQ ID NO: 3. Furthermore, none of the cited references, including Sherer et al., provide any suggestion or motivation to introduce lambda phage-HCV nucleic acid hybrids, such as that encoded by SEQ ID NO: 5, in a test sample to produce lambda phage-HCV amplicons. Moreover, none of the cited references provide any suggestion or motivation to introduce T7 RNA polymerase promoter-lambda phage-HCV nucleic acid hybrids, such as that encoded by SEQ ID NO: 4, in a test sample to produce lambda phage-HCV amplicons.

There is no reasonable expectation of success in making or using the presently claimed method. First, there is no reasonable expectation that the pair of primers disclosed in Resnick et al. would be successful in the TaqMan method described in Kleiber et al. and Kawai et al. As support, Applicants submit Wang et al. which states that "there is **no reliable means to** predict the sensitivity achieved by a given primer pair... some primer pairs, which have been designed taking into account the basic rules, **do not work** as efficiently **as expected**. **An extensive search** for optimal reaction protocol **may be unfruitful** with these primers" (p. 85, paragraph 5; emphasis added in bold). Moreover, Wang et al. explicitly states that "the reasons for such a difference in sensitivity between primer pairs **remains unanswered**" (see p. 87, paragraph 1; emphasis added in bold). Clearly, since there are no reliable means to predict which primer pair can be successfully employed in the detection of a given target nucleic acid and since there are no reasons which can explain the difference in sensitivity between primer pairs, there can be no reasonable expectation of success in substituting the pair of primers disclosed in Resnick et al. in the TaqMan method described in Kleiber et al. and Kawai et al.

The prior art references, taken singly or in combination, do not teach or suggest all the claim limitations. First, none of the cited references teach hybridizing HCV nucleic acids with an oligonucleotide probe consisting of the sequence set forth in SEQ ID NO: 3, as is recited in claim 1. Michinori et al. teaches a nucleotide sequence *comprising* SEQ ID NO: 3; however, the present claims explicitly recite "an oligonucleotide probe consisting of the sequence set forth in SEQ ID NO: 3." Secondly, none of the cited references, including Sherer et al., teach or suggest introducing lambda phage-HCV nucleic acid hybrids, such as that encoded by SEQ ID NO: 5, in a test sample to produce lambda phage-HCV amplicons, as is recited in claims 9, 14, 18, and 20. Moreover, none of the cited references teach or suggest introducing T7 RNA polymerase promoter-lambda phage-HCV nucleic acid hybrids, such as that encoded by SEQ ID NO: 4, in a test sample to produce lambda phage-HCV amplicons, as is recited in claims 15-18, 21 and 22.

Because no *prima facie* case of obviousness has been established, or, in the alternative, any *prima facie* case of obviousness that may have been established has been rebutted, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn or reversed.

CONCLUSION

In view of the foregoing remarks and amendments submitted herein, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

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